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Toxicology Update

Note: The Toxicology Update represents a brief review of an often extensive literature base. Only some of the directly related references may be included.

PERCHLORATES

Synonyms: Perchloric acid, sodium, potassium, lithium or ammonia perchlorate.

CAS no.: Ammonium perchlorate, 7790-98-7; lithium perchlorate, 7791-03-9; perchloric acid, 7601-90-3; potassium perchlorate, 7778-74-7; sodium perchlorate, 7601-89-0.

Boiling point: see Molecular formula.

Color: see Molecular formula.

DOT designation: Oxidizer, explosive, irritant.

Flammability limits: owing to their strong oxidizing ability, all perchlorates present a fire hazard when they are in contact with organic material or subjected to heat or shock.

Melting point: $HClO_4$, −112°C; NH_4ClO_4, decomposes with heating; $KClO_4$, 400°C (decomposes); $LiClO_4$, 230°C, decomposes at 430°C; $NaClO_4$, 482°C (decomposes).

Molecular formula: $HClO_4$—m.w. = 100, colorless, fuming hygroscopic material, $d = 1.764$, b.p. = 19°C. Commercial aqueous preparations are 65–70% solutions. $LiClO_4$—m.w. = 106, colorless crystals, $d = 2.429$. The hydrated form, $LiClO_4 \cdot 3HOH$, is also colorless, d = 1.84, m.p. = 75°C. NH_4ClO_4—m.w. = 117, white crystals, $d = 1.95$. $NaClO_4$—m.w. = 122, white, deliquescent crystals, $d = 2.02$. $KClO_4$—m.w. = 138, colorless crystals or white powder, decomposes by concussion, $d = 2.524$.

Odor: No odor for the perchlorates has been reported. NH_4ClO_4 imparts a bitter and salty taste to water. The threshold for taste in water is between 28 and 50 mg l^{-1} (av. = 45 mg l^{-1}), with the practical taste threshold between 56 and 90 mg l^{-1}.[15]

Water solubility: Perchloric acid and its salts are soluble in water. Potassium perchlorate is the least soluble salt. Some perchlorates are soluble in alcohols.

Specific gravity: NH_4ClO_4, 1.95; $LiClO_4$, 2.429; $HClO_4$, 1.764; $KClO_4$, 2.524; $NaClO_4$, 2.02. (References: 1–4 and 15.)

Composition

The perchlorate ion has been combined with one or more element of every group in the Periodic Table except the inert gases.[4] Commercial production of perchlorates is mostly by oxidizing sodium chloride electrolytically to sodium chlorate. Perchloric acid is produced by the direct electrolysis of cold hydrochloric acid. Ammonium perchlorate is prepared by the direct reaction of ammonia with perchloric acid.[5]

Uses

Perchloric acid and its salts are strong oxidizers and can ignite violently with combustibles. All perchlorates can find use in pyrotechnics, explosives and jet or rocket fuels. They can be used as catalysts or digesting agents in analytical chemistry laboratories, as etching and engraving agents, as an ingredient of electrolytic baths in depositing lead and electro-polishing and in the manufacture of various esters. Perchlorates can also be used in oxygen-generating devices for life-support systems in submarines, spaceships, bomb shelters and breathing apparatus.[5] Perchlorates are used in wooden and paper matches[6] and automobile air bags.[7]

Perchlorate salts have been used in medical practice as a provocative test for the release of thyroid hormones and therapeutically to treat specific categories of hyperthyroid conditions.[8,9]

Acute toxicity

The most significant hazard associated with perchlorate toxicity is the danger of fire or explosions. A mixture of mercuric hydroxide and perchloric acid spontaneously exploded when it was left to stand over the weekend, despite refrigeration.[10] Similarly, a solution of dimethylamine produced a violent explosion and fire when gently warmed in a vacuum.[11]

Mammalian testing on the perchlorates appears limited. Some of the reported toxicity values are presented in Table 1.

Ingestion. Ingestion of toxic doses of perchlorates leads to severe gastroenteric pain, vomiting and diarrhea. Respiratory distress may also develop owing to the conversion of hemoglobin to methemoglobin. The lethal oral dose for an adult is ca. 15 g or 0.214 g kg^{-1}.[12] Late toxic nephritis due to toxic doses of perchlorates has been reported.[13]

Ingestion of the acid can produce mild to moderately severe oral and esophageal burns, vomiting, drooling and pain. More severe burns can occur in the stomach but perforations are rare. The pyloric end of the stomach can undergo delayed stricture up to 3 weeks after ingestion. Hemolysis, acidosis and shock may be noted following significant acid ingestion.[17]

In acute toxicity testing, animals generally died within the first few days after oral administration of ammonium perchlorate. Autopsy findings included necrosis and hemorrhaging of the mucous membranes of the stomach. Animals that died within the first few days after ammonium perchlorate administration demonstrated intestinal damage, varying degrees of pulmonary edema, grey color tint to the liver and vascular dilation and congestion of the spleen, brain and sinuses.[15]

Rats administered potassium perchlorate in the drinking water at a concentration of 10 mg l^{-1} for 4 days did not show any significant changes in thyroid hormone levels. At the lowest effective concentration of 100 mg l^{-1} for 4–14 days there was a steady increase in thyroid-stimulating hormone (TSH) level in the serum and an insignificant increase in the serum levels of triiodothyronine (T_3) and thyroxine (T_4).[18]

Inhalation. The vapor pressure of perchlorate salts and acids is expected to be very low at normal temperatures. Therefore, exposure to fumes or vapors would be negligible. Exposure to mists or hot acid fumes can be expected to produce symptoms such as upper respiratory tract irritation, sneezing, coughing, dyspnea, chest pain and pulmonary edema. The onset of respiratory symptoms may be delayed for several hours. Any cyanosis is resistant to oxygen therapy due to methemoglobin formation.[17]

Eye contact. Owing to their high degree of water solubility and severe irritating properties, exposure to liquids, mists or dusts of the perchlorates can be expected to produce severe eye irritation characterized by lacrimation and conjunctivitis. Exposure to the acid form can result in pain, swelling, corneal erosions and blindness.[17]

Table 1. Toxicity values associated with perchlorate salts

Species/route of administration	Form	Type	Concentration (mg kg^{-1})
Rat/oral	NH_4^+	LD_{50}	4200–3500
Mouse/oral	NH_4^+	LD_{50}	1900–2000
Rabbit/oral	NH_4^+	LD_{50}	1900–750
Guinea pig	NH_4^+	LD_{50}	3310
Rabbit	NH_4^+	3 months	190 (nervous system effects)
Rat	NH_4^+	Chronic (9 months)	2[a] (thyroid activity)
Mouse/i.p.	Li^+	LD_{50}	1160
	Mg^{2+}	LD_{50}	1500
	Na^+	LD_{50}	1150
	Mn^{2+}	LD_{50}	410
	Fe^{3+}	LD_{50}	370
	Co^{2+}	LD_{50}	160
	Ni^{2+}	LD_{50}	100
	Cu^{2+}	LD_{50}	29
	Zn^{2+}	LD_{50}	76

[a] 0.25 mg kg^{-1} of 5 mg l^{-1} showed no effect.
(References: 7, 14–16.)

Skin contact. All perchlorates are strong oxidizers and skin irritants.[1] However, actual test scores with animal models could not be located in the literature.

Chronic toxicity

Ingestion. Potassium or sodium perchlorate has been used therapeutically to control thyroid abnormalities. Dose levels usually range between 600 mg to 1 g day^{-1}. Dose levels of 1 g day^{-1} have been used therapeutically to treat Graves' disease. No reported ill effects have been reported during such treatment for 22 years.[19] Similar treatment of hypothyroid patients for 2–6 months was also therapeutically effective in restoring the euthyroid state.[9] However, there are case reports of aplastic anemia[20] and liver degeneration[21] following perchlorate therapy for hyperthyroidism.

In a 9-month study, Shigan administered ammonium perchlorate to rats *per os*. Dose levels were 0.25, 2 and 40 mg kg^{-1}. The end point of assessment was the excretion of ^{131}I in the urine. The results indicate that there was no difference between the rats that served as the distilled water controls and those that received the 0.25 mg kg^{-1} ammonium perchlorate. There was also no difference in ^{131}I release in the two higher dose groups. However, there was a significant increase in iodine excretion between the 0.25-mg perchlorate dose group and the 2.0-mg perchlorate dose group[15] which demonstrates a steep dose–response curve.

Inhalation. See Acute toxicity, Inhalation.

Eye contact. See Acute toxicity, Eye contact.

Skin contact. See Acute toxicity, Skin contact.

Sensitization

No information regarding the sensitization potential of perchlorates was located in the available literature.

Target organ effects

Perchlorates have been shown to influence the iodine balance in the human thyroid gland.[22] The oral administration of 100 mg of $KClO_4$ results in a rapid discharge of trapped ^{131}I from the thyroid gland. This discharge is completed within 30 min. With lower doses, the iodide discharge was incomplete.[23]

There are several case history reports where the treatment of thyroid abnormalities with potassium perchlorate led to the onset of aplastic anemia.[24–28] Moderate SGOT and SGPT elevations have been reported following doses of 150–200 g of sodium perchlorate. Jaundice and hepatomegaly have also been reported.[17]

Administration of perchlorate salts to experimentals animals such as rats, mice and dogs demonstrated antithyroid actions[29] and induced abnormalities in hepatic, renal, cardiovascular and hemopoietic functions.[30,31] Hemolysis and methemoglobinemia have been reported following severe exposures. These effects may progress to subacute intravascular coagulation. Hyperkalemia secondary to hemolysis may occur and oliguria or anuria are common renal effects.[17]

Perchloric acid was found to inhibit aggregation and fusion of sheep erythrocytes incubated *in vitro* with 0.3 M sucrose and the absence of salts, surfactants, albumin and kinetic energy.[32]

Absorption–metabolism and excretion

The water solubility of the perchlorate salts would suggest that they may be readily absorbed from the gastrointestinal tract and excreted primarily via the urine. Pharmacological evaluations indicate that peak plasma levels occur about 3 h after oral administration. The perchlorate ion appears in the urine within 10–15 min after oral dosing.[23] It therefore appears that the perchlorate ions are not appreciably metabolized by humans.

There is a two-phase biological decay curve in animals for the perchlorate ion. In rats, the first biological half-life ranged from 1 to 2 h and accounted for ca. 96% of the dose. The second-phase half-life, which accounted for only 4% of the administered dose, ranged from 72 to 80 h. In calves, T_1 = 2–2.5 h and T_2 = 23–27 h.[33] All of the administered dose is excreted within 48–72 h.[34]

The administration of 500 mg kg^{-1} day^{-1} of sodium or ammonium perchlorate to rats for 45 days led to decreased carbohydrate and protein metabolism, decreased blood glucose levels, increased blood urea nitrogen and an increase in the plasma levels of cholesterol, phospholipids and lipoprotein profile.[35,36] Significant changes also occurred in the mucopolysaccharide and glycoprotein levels of the blood, lung, liver and salivary glands.[37] The activity of the Citric Acid Cycle enzymes decreased, as did the endogenous content of ATP of the mitochondria.[35] The activity of organ aldolase and lactic dehydrogenase increased as well as the level of liver arginase.[38] Other investigators noted decreased oxygen consumption and decreased regulatory thermogenesis with perchlorate treatment.[39,40]

The action of the perchlorate ion on the thyroid appears to include inhibition of iodine uptake by the cells of the thyroid and stimulation of release of thyroid hormones from the gland.[41,42]

Immunotoxicity

Symptoms suggestive of occupational asthma were seen in workers exposed to vapors of several mineral acids, including perchloric acid. Two out of twenty workers showed a reduction in FEV during the workshift. Five subjects

demonstrated bronchial hyperactivity.[43]

Although Graves' disease is currently believed to be an autoimmune disease[44] and the perchlorate ion has been successful in treating Graves' disease, Wenzel and Lente[8] reported that they could not find any evidence of an immunosuppressive effect of perchlorate on thyroid-stimulating immunoglobulin.

Reproductive toxicity

Developmental endocrine abnormalities have been reported for potassium perchlorate.[45] The TD_{Lo} (toxic dose, low) for such abnormalities in rabbits was 21.0 g kg^{-1} when administered between days 1 and 21 of pregnancy. Administration of 27.6 g kg^{-1} produces similar abnormalities when administered between days 1–9 in rats. In the guinea pig, 35.7 g kg^{-1} between days 48 and 68 of pregnancy caused developmental endocrine abnormalities.[45] A dose of 250 mg kg^{-1} day^{-1} had no effect on the normal pregnancy of the rat.[46] Chickens administered dose levels of 20–40 mg kg^{-1} demonstrated reduce body weight gain, disturbed feather development, failure to lose the 'chick' coloring, delayed sexual development and atresia of the thyroid gland and ovarian follicles and an increase in the number of degenerated Purkinje cells in the cerebellum.[47] The author of this latter study does not present sufficient information to allow a dose–response analysis.

Maternal administration of 1% $KClO_4$ (10 000 ppm) in the drinking water produced massive hyperplasia in fetal thyroids, indicating placental transfer of perchlorate ion. The estimated maternal dose of potassium perchlorate was 740 mg kg^{-1} day^{-1} and it had little to no effect on the maternal thyroid.[48] In rabbits, 100 mg kg^{-1} *per os* over the 28 days of pregnancy produced fetal as well as maternal goiters.[49]

In humans, untreated hypothyroidism in very young children leads to an irreversible condition called 'cretinism'. This state is characterized by dwarfing, mental retardation, protruding tongue and pot belly.[50]

Neurotoxicity

Lethargy, seizures and coma have been reported to be associated with perchlorate administration.[17] Ammonium perchlorate has been reported to induce a state of excitement, dyspnea, hind-limb twitching and convulsions at levels of 3500 mg kg^{-1} in the rat and 2000 mg kg^{-1} in the mouse.[15,45]

Genotoxicity

Sodium perchlorate is classified as a mutagen because it has been reported to affect DNA repair mechanisms in *E. coli* at a dose level of 1500 pmol per plate.[45] No other information regarding the genotoxicity of these perchlorates was found in the literature or databases searched.

Carcinogenicity

In a study on adverse effects of antithyroid compounds, potassium perchlorate was tested for tumor-promoting activity in rats. The animals were fed 1000 ppm potassium perchlorate at a ratio of 289 mg potassium perchlorate per 100 g of diaminodiphenylmethane (DHPN). The antithyroid compounds of potassium perchlorate, potassium iodide and propylthiouracil promoted the development of thyroid tumors in the rats treated with DHPN. Potassium perchlorate was a stronger promoter than propylthiouracil but potassium perchlorate alone did not induce any thyroid adenomas or cancers.[51]

Epidemiology

There are no reports that the ordinary occupational handling of the three common perchlorates, NH_4ClO_4, $NaClO_4$, $KClO_4$, has produced any serious health hazards other than the danger of flammability. There have been no reports of adverse health effects in long-term occupational exposures in perchlorate manufacturing plants.[5] No other information on the epidemiology of perchlorates could be located in the literature.

Environmental fate

Perchlorate dispersion through air would be accomplished through dusts or adsorption to dust particles. Owing to their water solubility, they would be mobile in soil and capable of migrating to groundwater. The water solubility also predicts that they will be rapidly dispersed in water. The perchlorate ion appears to be fairly stable in tapwater[15] but the oxidizing ability to these compounds predicts that they will react with organic material and be reduced to the chloride ion and oxygen. Ammonium perchlorate is not considered to be a persistent environmental chemical because the ammonium is subject to biodegradation and the perchlorate will slowly break down into chlorides.[52] This process is a stepwise reaction that occurs according to the following equations:

$$ClO_4^- \rightarrow ClO_3^- + 1/2\,O_2$$

$$ClO_3^- \rightarrow Cl^- + 3/2\,O_2$$

The overall reaction can be expressed as follows:

$$ClO_4^- \rightarrow Cl^- + 2O_2$$

When waste water containing an average concentration of 100 mg l^{-1} perchlorates was seeded with the anaerobic bacterium *Vibrio dechloraticans* Cuznesovei, the perchlorates were completely reduced to the chloride ion within 1 h.[53,54]

No studies on the bioaccumulation potential of the perchlorate ion in plants were found in the open literature.

Environmental toxicity

Perchlorates have been used as weed killers[55] as well as growth promoters in leguminous plants,[56] livestock (sheep and cattle) and poultry.[57] Soybeans were damaged when nurtured with water containing 2.5 ppm $KClO_4$ and significantly stunted at 5 ppm.[55] Maximum germination and enhanced growth was seen in wheat seedlings grown with an ammonium perchlorate solution of 1 ppm. Ammonium perchlorate also increased the germination rate for rye grass and cotton but the growth rate of the seedlings was inhibited at 55 ppb in the soil.[58] In animals, weight gain was increased by 3–31% by the addition of ammonium perchlorate to the feed. The optimum dose was given as 2–5 mg kg^{-1}. No negative effects were seen with doses up to ten times this level. This effect of ammonium perchlorate appears to be related to its thystatic activity.[5]

For the most part, the acute ecotoxicity of the perchlorate ion is quite low and many species can tolerate 1000 mg l^{-1} for up to 24 h. Tadpoles can survive indefinitely at concentrations of 500 mg l^{-1} but an antithyroidal effect that interferes with metamorphosis is noted. These antithyroidal effects can be observed at 36 mg l^{-1} in the nest and 70–90 mg l^{-1} perchlorate ion in the frog.[59]

Ecological testing on the different perchlorate salts has been conducted for different organisms (see Table 2).

Algae and bacteria are relatively insensitive to the perchlorate ion and some common bacteria are capable of metabolizing it. Based on the high tolerance of most of the ecosystem to this substance, it does not appear that the perchlorate ion is likely to become an environmental hazard.[59]

Regulatory status

There are no Occupational Safety and Health Administration (OSHA) standards on the use of perchlorates. Perchlorates and its specific salts are not listed in Table Z-1, CFR 29, 1900 to 1910. The American Conference of Governmental Industrial Hygienists (ACGIH) also does not list a TLV value for these substances.

Perchlorate-containing wastes are

Table 2. Some ecotoxicity values for perchlorate salts

X. laevis (tadpole)	K^+	Metamorphosis inhibition	500 ppm by immersion
R. temporaria (tadpoles)	K^+	Metamorphosis inhibition	500 ppm by immersion
D. magna	Na^+	LC_{50} (24 h)	940 ppm
		LC_0	630 ppm
C. auratus (goldfish)	Na^+	Acute toxicity	NOEL = 800 ppm = 1000 ppm/3 days
L. reticulatus (guppy)	K^+	Chronic toxicity	500 ppm Thyroid effects Arrested sexual development
S. gairdinerli (rainbow trout).	NH_4^+	LC_{50} (24 h)	650 ppm
		LC_{50} (96 h)	400 ppm
D. magna	K^+	EC_{50} (24 h) for acute toxicity	1077 ppm
		EC_{50} (24 h) for immobilization	803 ppm
D. magna	NH_4^+	LC_{50} (24 h)	540 ppm
		LC_{50} (48 h)	290 ppm
D. magna	NH_4^+	LC_{50} (31 days)	73 ppm
		LC_0	20 ppm
D. pulex	NH_4^+	LC_{50} (n.o.s.)*	75–325 ppm
		EC for ovogenesis suppression	10–50 ppm
Soybean	NH_4^+	Toxic expression	2.5 mg l^{-1}
Bluegreen/ green algae	K^+	Inhibition	79/359 mg l^{-1}

* n.o.s. = not otherwise specified.
(References: 14, 59–63.)
EC = effective concentration.

considered hazardous wastes by the California Code of Regulations (CCR). Title 22, Article 9, Section 66680 lists ammonium perchlorate as ignitable and reactive. Perchloric acids is listed as toxic, corrosive, ignitable and reactive. Potassium and sodium perchlorates are considered toxic, reactive and ignitable. Lithium perchlorate is not listed.

No other regulations governing perchlorate compounds were located.

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